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Award Number: W81XWH-13-2-0009

TITLE: Treating Intractable Post-Amputation Phantom Limb Pain With Ambulatory Continuous Peripheral Nerve Blocks

PRINCIPAL INVESTIGATOR: Brian M. Ilfeld, MD, MS

CONTRACTING ORGANIZATION: University of California, San Diego, San Diego, CA 92103-8770

REPORT DATE: January 2014

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
January-2014	Annual	26 December 2012–25 December 2013

4. TITLE AND SUBTITLE
Treating Intractable Post-Amputation Phantom Limb Pain With Ambulatory Continuous Peripheral Nerve Blocks

5a. CONTRACT NUMBER
W81XWH-13-2-0009

5b. GRANT NUMBER
W81XWH-13-2-0009

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Principal Investigator Brian M. Ilfeld, MD, MS
Research Manager Anya Morgan, MA, CCRC

E-Mail: Anya Morgan: acmorgan@ucsd.edu; Brian Ilfeld bilfeld@ucsd.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of California, San Diego
200 West Arbor Dr MC 8770
San Diego, CA 92103-8770

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT (brief – 200 words approx.) of most significant finding during the research period.

The goals and tasks of Funding Year 1 encompassed multiple regulatory approvals and study start-up activities:

- The Data Safety Monitoring Board was established and the Charter approved by all members
- The study protocol and all data forms were finalized
- Research manager, coordinators, and relevant personnel were hired/existing personnel trained at all collaborating sites
- The Principal Investigator and UCSD trial manager conducted required site visits with WRNMMC, Cleveland Clinic, and Palo Alto VA (NMCSD pending IRB approval)
- UCSD, the coordinating center, received local and USAMRMC regulatory approval
- Two collaborating sites, WRNMMC and Cleveland Clinic, received local and USAMRMC regulatory approval
- Palo Alto VA received local IRB approval from one of its two required IRBs, and initiated submission to USAMRMC
- NMCSD completed its local regulatory submission, approval pending
- Data-entry platform was developed and is active
- Equipment was identified, ordered, and received
- First study subject was successfully enrolled and data collection begun at UCSD

15. SUBJECT TERMS none provided					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U	UU	15	19b. TELEPHONE NUMBER *(include area code)*

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Introduction:

This project is a randomized, double-masked, placebo-controlled, simultaneous parallel and crossover, human-subjects clinical trial to determine if ambulatory continuous peripheral nerve block (CPNB) is an effective treatment for intractable phantom limb pain following a traumatic limb amputation. There is currently no reliable treatment for phantom limb pain, which resolves in only 16% of cases. This is a multicenter trial at five collaborating sites: Walter Reed National Military Medical Center, Naval Medical Center San Diego, Veterans Affairs Palo Alto, Cleveland Clinic, and the University of California, San Diego. Subjects will have an existing upper or lower amputation and experience phantom limb pain at least 3X per week for the previous 8 weeks. They will be randomized to receive one of two study solutions in a double-masked manner: either a local anesthetic (ropivacaine 0.5%) or placebo (normal saline). Catheters will be removed after 6 days of at-home infusion. Although not required, each subject has the option to return for the alternative treatment 4-16 weeks later (crossover infusion). The primary endpoint will be the difference in average phantom pain intensity at baseline and 4 weeks following the initial infusion as measured with the Numeric Rating Scale between treatment groups for the initial infusion. Secondary endpoints will involve intra- and inter-subject comparisons of additional measures of pain and health-related quality-of-life. This trial has a strong potential to identify the first reliably effective treatment for intractable phantom limb pain following a traumatic limb amputation.

Body:

Statement of Work for Funding Year 1

Funding Year:	1		
Months (Within	1-4	5-8	9-12
Register study on clinicaltrials.gov	x		
Initiate DSMB meetings	x		
DSMB meetings (every 6 months)		x	x
Report to medical monitor (every month)		x	x
Finalize protocol and study forms	x		
Hire/train research coordinators	x	x	x
Site visits and training by UCSD coordinator	x		
Submit study to individual IRBs and	x	x	
Site visits and training by Principal		x	
Prepare data-entry platform at UCSD	x		
Send database letters (following IRB		x	x
Educate clinic contacts for referrals		x	x
Order and prepare equipment	x	x	
Amputee support group outreach			x
Advertising study in publications/websites			x
Patient enrollment (following IRB approval)			x
Quality assurance			x
Interim analyses (at 25%, 50%, 75%			
Data collection & entry (Day 1 to Month 12)			x
Data cleaning and final statistical analysis			
Manuscript preparation: protocol			
Manuscript preparation: final results			
IRB closures at all enrolling centers			
Final report to USAMRMC			
Uploading results to ClinicalTrials.gov			
Results sent to all enrolled subjects			

The following is a report on each task listed in the above Statement of Work for Funding Year 1.

Tasks

1. Register study on clinical trials.gov

The project was registered and released to the public during the 1st quarter, as scheduled.

2. Initiate DSMB meetings
The Data Safety Monitoring Board was established and the Charter approved by all members, after a revision process culminating in a preliminary meeting via conference call on September 18, 2013.

3. DSMB Meetings every 6 months

A calendar of reports and regular meetings has been agreed on. The first regular meeting will occur within six months of the date the fist subject was enrolled, December 16, 2013.

4. Report to medical monitor (every month)
The medical monitor was notified of the first subject enrollment during the 4th Quarter.

5. Finalize protocol and study forms
After review by steering committee members, members of the DSMB, and the Site Directors, the protocol was finalized, including one substantive change to inclusion criteria. Adjustments to the Summary of Post-Enrollment Assessments were also made to capture data at additional timepoints. In addition, a different center was selected to develop the study database and this change was reflected in the finalized protocol. Other changes were minor and not substantive.

The finalized protocol was fitted to the University of California at San Diego (the coordinating center) template, and sent to the four collaborating sites to be used for their local IRB submissions, and sent to the USAMRMC to be reviewed. It was subsequently approved without revision by the USAMRMC.

Trial monitor and PI developed ten data forms in total to be used to capture all data needed according the study protocol. These data forms incorporate the four questionnaires used in the study. The data forms were approved by the USAMRMC and sent to all the sites to assist with their regulatory submissions.

6. Hire/train research coordinators
The UCSD coordinating center hired the trial monitor/project manager to coordinate enrollment at UCSD and manage the overall study. Ms. Morgan was hired January 3, approximately two weeks after the grant period began on December 26, 2012. Ms. Morgan was trained on the protocol by the principal investigator and is managing the regulatory processes and work described in this report.

Each site has trained the appropriate personnel to implement the study.

7. Site visits and training by UCSD coordinator
The Statement of Work states that the site visits and training by the principal investigator and UCSD trial manager will occur in different quarters, but the visits

were conducted by both the PI and the UCSD trial manager, within the 3rd and 4th quarters, based on each site's projected IRB approval date. The principal investigator and trial manager conducted site visits together on the following dates:
October 25, 2013: Cleveland Clinic
November 22, 2013: Palo Alto Veteran's Affairs
December 13, 2013: Walter Reed National Military Medical Center

The site visit for the Naval Medical Center San Diego is pending their IRB approval. The Naval Medical Center anticipates IRB approval within the first quarter of Funding Year 2, and the site visit will be conducted at that time.

During the site visits, the PI and UCSD manager met with the site director, the regulatory personnel, research coordinators and assistants, and the investigational drug pharmacist. The site directors were trained on all aspects of the protocol and intervention by the PI. Other research personnel were trained on the protocol and all aspects of recruitment, informed consent, enrollment, and case report forms completion by the trial manager.

8. Submit study to individual IRBS and USAMRMC

The University of California, San Diego Institutional Review Board reviewed and approved this project on April 4, 2013, pending minor revisions and clarifications, which were provided on April 22, 2013. In addition, revisions to the consent requested by the Human Subjects Protection Scientist, Ms. Melanie Frank, were submitted along with the USAMRMC HRPO approved protocol to the UCSD IRB on June 3, 2013. All final documents were reviewed at the regular UCSD IRB meeting on June 6, 2013, and approved. The approval was backdated to the initial approval date of April 4, 2013, per the UCSD IRB policy.

During the administrative review, Ms. Frank requested that requested that the FDA be contacted to evaluate whether or not an Investigational New Drug Application would be necessary to conduct the trial. A submission was made to the FDA to formally request an evaluation for an IND; it was received in the Center for Drug Evaluation and Research on May 8, 2013. The FDA determined on May 13, 2013, that an IND is not necessary; the PI received a letter describing the conclusions on May 18, 2013. For archival and documentation purposes, a Pre-IND number was assigned to track the evaluation: #118546. The reference number for the submission is: #3307577.

In addition, the USAMRMC HRPO asked for a determination from the IRBs at Wake Forest University and Johns Hopkins University regarding whether or not the participation of the steering committee members from those universities constituted participation in human subjects research. A determination was requested and both IRBs determined that the steering committee members' actions did not constitute engaging in human subjects research and therefore IRB review is

not required from those institutions.

The UCSD IRB met and reviewed the revisions on June 6, 2013 and final study approval was released on June 14, 2013. The approved, stamped consent was released and sent to the PI and trial monitor on June 24, 2013. Per instructions from the USAMRMC administrative reviewer, Ms. Melanie Frank, the approved, stamped consent, flyer, recruitment letter, HIPAA, and protocol were sent to her attention for final review. Final regulatory approval from the USAMRMC ORP HRPO was issued on July 26, 2013.

Cleveland Clinic received local IRB approval during the 2nd quarter, completed its regulatory submission to the USAMRMC during the 3rd quarter, and received regulatory approval to begin enrollment from the USAMRMC on September 9, 2013.

Walter Reed National Military Medical Center received local IRB approval and completed its regulatory submission to the USAMRMC during the 3rd quarter, and received regulatory approval from the USAMRMC to begin enrollment on December 19, 2013.

Palo Alto Veterans Affairs is required to seek regulatory approval from its collaborating Stanford IRB, as well the VA IRB, on this project. Stanford IRB approval was received on August 13, 2013. Palo Alto initiated its submission to the USAMRMC during the 4th quarter. Approval is pending the receipt of VA IRB approval; this is anticipated the 1st quarter of Funding Year 2.

Naval Medical Center submitted to their Scientific Review Committee and was approved by that committee on June 7, 2013. The complete package was submitted to their IRB on June 12, 2013 and approval remains pending, due to rescheduled IRB meetings, and subsequent minor revision requests. Approval is anticipated during the 1st quarter of Funding Year 2.

9. Site visits and training by Principal Investigator
This task was described in #7.

10. Prepare data-entry platform at UCSD
The UCSD trial manager initially contacted the Clinical Translational Research Institute (CTRI) at UCSD, per the original plan in the grant, to develop the trial's data-entry platform. The CTRI had originally stated that they would collaborate to develop the trial database using a relational electronic data capture system referred to as RedCAP. When approached by the trial monitor, the CTRI stated that they no longer provided support for the RedCAP system, and had switched to an alternative system. After analyzing the needs of the study and the capabilities of the other sites, the PI selected the Cleveland Clinic to develop and host the RedCAP database for the project. Cleveland Clinic has a full-time RedCAP programmer to

develop the database in collaboration with the UCSD coordinating center.
The data-entry platform was completed on May 20, 2013. The finalized CRFs were inputted into the database production environment. The calendar was set up, and the UCSD trial monitor and the PI received log-in IDs and passwords. The trial monitor has received training in database use, including data entry and report generation. As part of the database development in conjunction with the required regulatory process at WRNMMC, a System Security Verification application was completed by the database manager and UCSD trial monitor and was approved by WRNMMC

11. Send database letters (following IRB approval)
The goal of this task is to compile a list of amputees from various sources and send them letters informing them of the study inviting them to contact study personnel if they desire to participate. This task has been moved to Funding Year 2, when all sites are approved for enrollment

12. Educate clinic contacts for referrals
Cleveland Clinic and WRNMMC confirmed during the site visits and by subsequent email contact that they have begun the process of educating clinic contacts and personnel regarding the study during the 4th quarter of Funding Year 1 and will continue into Funding Year 2. The UCSD manager will visit local clinics for this purpose during Funding Year 2. The Naval Medical Center will begin this process once local IRB approval is obtained, anticipated during the 1st quarter of Funding Year 2.

13. Order and prepare equipment
Necessary equipment and companies from where equipment will be obtained was identified. The necessary financial infrastructure was set up to create purchase orders (an index has been created for the trial). Supplies and drug and been ordered and received.

14. Amputee support group outreach
A recruitment plan has been developed for use at UCSD based on the original recruitment plan in the grant application. Specific leaders of amputee groups and contacts in advertising and recruitment for local and national amputee groups have been identified. Recruitment plan will be implemented during Funding Year 2.

15. Advertising study in publications/websites
Please see #14.

16. Patient enrollment (following IRB approval)
The first subject was successfully enrolled on December 16, 2013.

17. Quality assurance
Quality assurance is ongoing with regard to subject data.

18. Data collection (Day 1 to Month 12)
Data collection was successfully begun with the participation of the first subject on December 16, 2013.

Key Research Accomplishments:

- The Data Safety Monitoring Board was established and the Charter approved by all members
- The study protocol and all data forms were finalized
- Research manager, coordinators, and relevant personnel were hired/existing personnel trained at all collaborating sites
- The Principal Investigator and UCSD trial manager conducted required site visits with WRNMMC, Cleveland Clinic, and Palo Alto VA (NMCSD pending IRB approval)
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Reportable Outcomes:
Non-applicable. The goals and tasks of Funding Year 1 encompassed multiple regulatory approvals and study start-up activities.

Conclusion:
This is a randomized, triple-masked, placebo-controlled clinical trial that will remain masked until enrollment is completed and the final value for the primary endpoint has been collected. We have just begun enrollment; and, therefore, no results are available at this time. However, we have enrolled our initial subject and the protocol worked as planned, with no revisions required.

References:
Non-applicable

Appendices:
Study questionnaires are attached on the following pages 8-11.

Beck Depression Inventory: Day 0
(Initial or Crossover Treatment)

Randomization Number: ____ - ____ - ____ ____ ____ *[fill in following randomization]*

Subject Initials: ____ ____ ____

Administered by (initials): ___ ___

Questionnaire Date: ____ / ____ / 201 ____

Time point: □ Initial □ Crossover

Circle the correct number for each question:

1) Sadness:
0 You do not feel sad.
1 You feel sad much of the time
2 You are sad all the time.
3 You are so sad or unhappy that you can't stand it

2) Pessimism:
0 You are not discouraged about your future.
1 You feel more discouraged about your future than you used to be.
2 You do not expect things to work out for yourself.
3 You feel your future is hopeless and will only get worse.

3) Past Failure:
0 You do not feel like a failure.
1 You have failed more than you should have
2 As you look back, you see a lot of failures.
3 You feel you are a total failure as a person.

4) Loss of Pleasure:
0 You get as much pleasure as you ever did from things you enjoy.
1 You don't enjoy things as much as you used to.
2 You get very little pleasure from the things you used to enjoy.
3 You can't get any pleasure from the things you used to enjoy.

[Continued on following page]

5) Guilty Feelings:
0 You don't feel particularly guilty.
1 You feel guilty over many things you have done or should have done.
2 You feel quite guilty most of the time.
3 You feel guilty all the time.

6) Punishment Feelings:
0 You don't feel you are being punished.
1 You feel you may be punished.
2 You expect to be punished.
3 You feel you are being punished.

7) Self-Dislike:
0 You do not feel sad.
1 You feel sad much of the time.
2 You are sad all the time.
3 You are so sad or unhappy that you can't stand it.

8) Self-Criticalness:
0 You don't criticize or blame yourself more than usual.
1 You are more critical of yourself than you used to be.
2 You criticize yourself for all of your faults.
3 You blame yourself for everything bad that happens

9) Suicidal Thoughts or Wishes:
0 You don't have any thoughts of killing yourself.
1 You have thoughts of killing yourself, but you would not carry them out. *
2 You would like to kill yourself. *
3 You would kill yourself if you had the chance. *
*contact Site Director at end of questionnaire

10) Self-Dislike:

0 You don't cry any more than you used to.
1 You cry more than you used to.
2 You cry over every little thing.
3 You feel like crying, but you can't.

11) Agitation:

0 You are no more restless or wound up than usual.
1 You feel more restless or wound up than usual.
2 You are so restless or agitated that it's hard to stay still.
3 You are so restless or agitated that you have to keep moving or doing something.

12) Loss of Interest:

0 You have not lost interest in other people or activities.
1 You are less interested in other people or things than before.
2 You have lost most of your interest in other people or things.
3 It's hard to get interested in anything.

13) Indecisiveness:

0 You make decisions about as well as ever.
1 You find it more difficult to make decisions than usual.
2 You have much greater difficulty in making decisions than you used to.
3 You have trouble making any decisions.

14) Worthlessness:

0 You do not feel you are worthless.
1 You don't consider yourself as worthwhile and useful as you used to.
2 You feel more worthless as compared to other people.
3 You feel utterly worthless.

15) Loss of Energy:

0 You have as much energy as ever.
1 You have less energy than you used to have.
2 You don't have enough energy to do very much. 3 You don't have enough energy to do anything.

16) Changes in Sleeping Pattern:

0 You have not experienced any change in your sleeping pattern.
1a You sleep somewhat more than usual.
1b You sleep somewhat less than usual.
2a You sleep a lot more than usual.
2b You sleep a lot less than usual.
3a You sleep most of the day.
3b You wake up 1-2 hours early and can't get back to sleep.

17) Irritability:

0 You are no more irritable than usual.
1 You are more irritable than usual.
2 You are much more irritable than usual.
3 You are irritable all the time.

18) Changes in Appetite:

0 You have not experienced any change in appetite.
1a Your appetite is somewhat less than usual.
1b Your appetite is somewhat greater than usual.
2a Your appetite is much less than before.
2b Your appetite is much greater than usual.
3a You have no appetite at all.
3b You crave food all the time.

19) Concentration Difficulty:

0 You can concentrate as well as ever.
1 You can't concentrate as well as usual.
2 It's hard to keep your mind on anything for very long.
3 You find you can't concentrate on anything.

20) Tiredness of Fatigue:

0 You are no more tired or fatigued than usual.
1 You get more tired or fatigued more easily than usual.
2 You are too tired or fatigued to do a lot of the things you used to do.
3 You are too tired or fatigued to do most of the things you used to do.

21) Loss of Interest in Sex:

0 You have not noticed any recent change in your interest in sex.
1 You are less interested in sex than you used to be.
2 You are much less interested in sex now.
3 You have lost interest in sex completely

Data Collection Form: Day 28
(Initial or Crossover Treatment)

Randomization Number: ____ - ____ - ____ ____ ____

Subject Initials: ____ ____ ____

Treatment: ☐ Initial ☐ Crossover

Administered by (initials): ___ ___

Questionnaire Date: ____ / ____ / 201 ____

Read aloud: *I am going to ask you some questions referring to pain in your limb being treated. Stump pain is defined as painful sensations located in the portion of the limb still physically present. Phantom limb pain is defined as painful sensations experienced where there is no longer a limb. First, I will ask you about any* ***phantom limb pain*** *you may be having.*

On a scale from 0-10, with 0 equal to 'no pain' and 10 equal to 'worst imaginable pain':

1a) How would you describe your phantom limb pain at its WORST in the last three days? ____ ____

2a) How would you describe your phantom limb pain at its LEAST in the last three days? ____ ____

3a) How would you describe your phantom limb pain on AVERAGE in the last three days? ____ ____

4a) How would you describe how much phantom limb pain you have RIGHT NOW? ____ ____

The next questions use the same 0-10 scale, but now refer to your RESIDUAL LIMB or STUMP pain:

1b) How would you describe your stump pain at its WORST in the last three days? ____ ____

2b) How would you describe your stump pain at its LEAST in the last three days? ____ ____

3b) How would you describe your stump pain on AVERAGE in the last three days? ____ ____

4b) How would you describe how much stump pain you have RIGHT NOW? ____ ____

On a scale from 0%-100%, with 0% equal to 'no relief' and 100% equal to 'complete relief':

How much relief have pain treatments or medications provided in the last three days for your:

5a) PHANTOM LIMB pain? ____ ____ ____ %

5b) STUMP pain? ____ ____ ____ %

The next questions refer only to your phantom limb pain. On a scale from 0-10, with 0 equal to 'does not interfere' and 10 equal to 'completely interferes':

In the last three days, how has your *phantom limb pain* interfered with [must answer all]:

6a) General Activity ____ ____

7a) Mood ____ ____

8a) Walking ability ____ ____

9a) Normal work (includes both work outside the home and housework) ____ ____

10a) Relations with other people ____ ____

11a) Sleep ____ ____

12a) Enjoyment of life ____ ____

Patient Global Impression of Change Scale (PGIC)

How much improvement you have had in your phantom limb pain ***since the very first catheter was placed****:*

Very much worse			No change			Very much improved
1	2	3	4	5	6	7

Now, I am going to ask about the frequency and duration of phantom limb pain [record "99" for continuous]**.**

13a) How many times in the last three days have you experienced **phantom limb** pain? ____ ____

14a) How many minutes/hours did each episode last, on average (circle m/h): ____ ____ min / hour

13c) How many times in the last three days have you experienced **non-painful phantom sensations** in the lost body part? ____ ____

14c) How many minutes/hours did each episode last, on average (circle m/h): ____ ____ min / hour

6b) How many times in the last three days have you experienced **stump** pain? ____ ____

7b) How many minutes/hours did each episode last, on average (circle m/h): ____ ____ min / hour

Which study fluid do you believe you received during your most-recent infusion:

☐ Definitely active ☐ Probably active ☐ Don't know ☐ Probably saline ☐ Definitely saline